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HIV/HCV coinfection model: a fractional-order perspective for the effect of the HIV viral load

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Abstract

We study the burden of the HIV viremia and of treatment efficacy in the severity of the patterns of the HIV/HCV coinfection. For this, we derive a simple non-integer-order (fractional-order) model for the coinfection dynamics. Fractional-order models have been proved in the literature to provide good fits to real data from patients suffering from several diseases, such as HIV, dengue fever, and others. We have computed the basic reproduction number and the stability of the disease-free equilibrium of the model. The numerical results suggest that the HIV viral load impacts impressively the severity of the HCV infection. The treatment efficacy is also found to influence the natural progression of HCV on the HIV/HCV coinfection. The latter is repeated for all values of the order of the fractional derivative. Moreover, the fractional derivative may pave the way to better understanding the individuals' patients' adjustments to treatment and to viremia.

Keywords: coinfection; HIV; HCV; fractional order; treatment

1 Introduction

The human immunodeficiency virus (HIV) and the hepatitis C virus (HCV) infections are major global public health issues. There are 37 million people infected with HIV worldwide, and about 115 million people HCV antibody positive. One-third of HIV-infected patients are infected with HCV [1]. People coinfected with HIV and HCV are prone to a faster development of HCV infection [1], presenting higher HCV viral loads, and they are more efficient in transmitting HCV [2]. Moreover, the spontaneous elimination of HCV is also decreased in untreated HIV coinfected patients [2]. One of the leading causes of death in HIV treated coinfected patients is chronic HCV infection [3], due to drug-related hepatoxicity. On the other hand, there is evidence that treatment of HIV can slow the natural progression of HCV infection and reduce HCV mortality related to liver diseases [1].

The last few decades have been rewarding in terms of the appearance of a significant diversity of useful mathematical models for the understanding of HIV and HCV coinfection. In 2012, Alexander *et al.* [4] proposed a model for drug resistance in patients with a chronic viral disease, such as HIV or HCV. They derived dependencies between the parameters of the system that are important factors in driving drug resistance. In 2012, Rong *et al.* [5] presented a mathematical model of two virus strains, one sensitive and one resistant, to HCV drugs. They provided a theoretical framework to explore the prevalence

of pre-existing mutant variants and the evolution of drug resistance during HCV treatment. In 2015, Birger *et al.* [6] improved an existing model for HCV infection to include the dynamics of the HIV and HCV coinfection, where an immune system component for infection clearance is incorporated. They found that the progression of HCV infection is more rapid when the immune response is compromised by HIV. A better understanding of the mechanisms behind this immune impairment in coinfection may help to devise better therapeutic regimens and to identify patients more compliant to certain drugs.

1.1 Fractional calculus: brief summary

Lagrange and Leibniz were the first mathematicians exchanging letters about the possible meaning of a 1/2-order derivative. They were the predecessors of non-integer-order differentiation and integration, also known as fractional calculus (FC). FC has had a huge development in the last few decades and notable work has been published in engineering, namely electronics, viscoelasticity, biology, physics, epidemiology [7–16].

In 2012 [17], Yan *et al.* proposed a fractional-order (FO) model for HIV infection with time delay. They compute the stability of the disease-free and of the endemic equilibria and enumerate conditions on the value of the delay, to ensure the asymptotic stability of the two equilibria. In [18] the role of treatment in a FO model was considered for HIV-1 dynamics. In [19], numerical outcomes of a FO model for HIV epidemics were fitted to data from 10 HIV patients. The FO model provides a better fit than the integer-order model. Diethelm [20] introduced a FO model for the patterns of dengue fever. Simulations of the model are fitted to real data of the 2009 dengue outbreak in Cape Verde, providing good agreement. Rihan *et al.* [15] proposed a FO SIRC epidemic model for the infection by Salmonella bacteria. The variation of the reproduction number was analyzed with respect to contact rate, recovery rate, and other parameters relevant parameters. An unconditionally stable numerical method to approximate the numerical solutions of the FO model was proposed. In [16], a FO model of predator-prey with type-II Holling functional response and time delay is introduced. The fractional derivative improves the stability of the solutions and provides faster transients of the solutions. The authors concluded that the FO models are more suitable to model biological systems with memory, than their integer-order counterparts. Pinto *et al.* [21] proposed a fractional complex-order model of drug resistance in HIV dynamics. The authors conclude that the complex-order derivative may be interpreted as the delay in the integer-order systems.

Fractional-order systems have been applied in the literature with the purpose of obtaining a deeper understanding of the complex behavioral patterns of biological systems. The memory property of the fractional models allows the integration of more information from the past, which translates in more accurate predictions for the model. With respect to the epidemiological models, this memory property may be used to devise adequate therapeutics directed to each individual, since distinct patients present different disease progression routes. The latter are associated with age, status of the immune system, and genetic profile. Clinicians can, thus, use the information (in terms of behavior's predictions) of fractional-order systems to fit patients data with the most appropriate non-integer-order index.

With the aforementioned ideas in mind, we derive a fractional-order model for HIV and HCV coinfection, where treatment for HCV is included. The model is an adaptation of two previous integer-order models for HCV mono-infection. In Section 2, we derive

the model. In Section 3, we compute the basic reproduction number of the model and the stability of the disease-free equilibrium. The simulations of the model are discussed in Section 4. Finally, the study is concluded in Section 5.

2 Model

In this section, we describe the HIV and HCV coinfection model. The population of the model is divided in six classes, namely the uninfected hepatocyte, x, the drug-sensitive infected hepatocytes, y_s, the drug-resistance infected hepatocytes, y_r, the drug-sensitive HCV virus, v_s, the drug-resistance HCV virus, v_r and the CD4$^+$ T cells, H.

The uninfected hepatocytes are produced at a rate λ^α and die at a rate d^α. These cells reproduce at rate r_1^α. Parameter $T_{\max}$ is the maximum capacity number of the hepatocytes. The uninfected hepatocytes, x, are infected when in contact with drug-sensitive virus, v_s, and when in contact with drug-resistant virus, v_r, at rates β_s^α and β_r^α, respectively. The drug-sensitive and drug-resistance infected hepatocytes die, respectively, at rates a_s^α and a_r^α. The HCV sensitive and resistant virus, v_s and v_r, are produced by the corresponding infected hepatocytes classes, y_s and y_r, at rates k_s^α and k_r^α. They die at rates c_s^α and c_r^α, respectively. The CD4$^+$ T cells are recruited at rate s_H^α and die at rate d_H^α. These cells are infected when in contact with HIV virus, V_H, at rate β_H^α. The parameter α_1 models the dependence of the HCV clearance rate on the CD4$^+$ T cells count. The dependence of the CD4$^+$ T cells activation rate on the HCV infected cell count is given by the parameter γ. The mutation rates are modeled by parameters u_I and u_P, where u_I is the mutation at the infection step and u_P at the virion production step.

Treatment is considered at two steps of the replication cycle. A first drug blocks the infection of target cells, through reverse transcriptase or integrase inhibitors, which reduce the successful infection rate of the sensitive strain by a factor ϵ_I, called the efficacy. A second drug, such as a protease inhibitor, prevents the production of viable virions, with efficacy ϵ_P.

The nonlinear system of fractional-order differential equations describing the dynamics of the model is

$$\begin{aligned}
&\frac{d^\alpha x}{dt^\alpha} = \lambda^\alpha - d^\alpha x - \beta_s^\alpha(1-\epsilon_I)xv_s - \beta_r^\alpha xv_r + r_1^\alpha x\left(1 - \frac{x+y_s+y_r}{T_{\max}}\right),\\
&\frac{d^\alpha y_s}{dt^\alpha} = \beta_s^\alpha(1-\epsilon_I)(1-u_I)xv_s - a_s^\alpha(1+\alpha_1 H)y_s,\\
&\frac{d^\alpha y_r}{dt^\alpha} = \beta_s^\alpha(1-\epsilon_I)u_I xv_s + \beta_r^\alpha xv_r - a_r^\alpha(1+\alpha_1 H)y_r,\\
&\frac{d^\alpha v_s}{dt^\alpha} = k_s^\alpha(1-\epsilon_P)(1-u_P)y_s - c_s^\alpha v_s,\\
&\frac{d^\alpha v_r}{dt^\alpha} = k_s^\alpha(1-\epsilon_P)u_P y_s + k_r^\alpha y_r - c_r^\alpha v_r,\\
&\frac{d^\alpha H}{dt^\alpha} = s_H^\alpha\big(1+\gamma(y_s+y_r)\big) - d_H^\alpha H - \beta_H^\alpha V_H H,
\end{aligned} \tag{1}$$

where $\alpha \in (0,1]$ is the order of the fractional derivative. When $\alpha = 1$, then the model is the integer-order counterpart. The fractional derivative of the proposed model is used in the

Caputo sense, *i.e.*,

$$\frac{d^{\alpha}y(t)}{dt^{\alpha}} = I^{p-\alpha}y^{(p)}(t), \quad t > 0,$$

where $p = [\alpha]$ is the value of α rounded up to the nearest integer, $y^{(p)}$ is the pth derivative of $y(r)$, I^{p_1} is the Riemann-Liouville fractional integral given by

$$I^{p_1}z(t) = \frac{1}{\Gamma(p_1)}\int_0^t \left(t-t'\right)^{p_1-1}z\left(t'\right)dt'.$$

2.1 Non-negative solutions

In this section we prove the positivity of the solutions of model (1).

Let $R_+^6 = \{w \in R^6 \mid w \geq 0\}$ and $w(t) = (x(t), y_s(t), y_r(t), v_s(t), v_r(t), H(t))^T$.

To prove the main theorem, we need the following generalized mean value theorem [22] and corollary.

Lemma 1 ([22]) *Suppose that $f(w) \in C[a,b]$ and $D_a^{\alpha}f(w) \in C(a,b]$, for $0 < \alpha \leq 1$, then we have*

$$f(w) = f(a) + \frac{1}{\Gamma(\alpha)}\left(D_a^{\alpha}f\right)(\xi)(w-a)^{\alpha} \tag{2}$$

with $a \leq \xi \leq w$, $\forall w \in (a,b]$ and $\Gamma(\cdot)$ is the gamma function.

Corollary 2 *Suppose that $f(w) \in C[a,b]$ and $D_a^{\alpha}f(w) \in C(a,b]$, for $0 < \alpha \leq 1$. If $D_a^{\alpha}f(w) \geq 0$, $\forall w \in (a,b)$, then $f(w)$ is non-decreasing for each $w \in [a,b]$. If $D_a^{\alpha} \leq 0$, $\forall w \in (a,b)$, then $f(w)$ is non-increasing for each $w \in [a,b]$.*

We now prove the main theorem.

Theorem 3 *There is a unique solution $w(t) = (x(t), y_s(t), y_r(t), v_s(t), v_r(t), H(t))^T$ to model (1) on $t \geq 0$ and the solution will remain in R_+^6.*

Proof From Theorem 3.1 and Remark 3.2 of [23], we know the solution on $(0, +\infty)$ of the initial value problem exists and is unique. We now prove that the non-negative orthant R_+^6 is a positively invariant region. To do this, we need to show that on each hyperplane bounding the non-negative orthant, the vector field points to R_+^6. From model (1), we find

$$\begin{aligned}
&D^{\alpha}x|_{x=0} = \lambda^{\alpha} \geq 0, \qquad D^{\alpha}y_s|_{y_s=0} = \beta_s^{\alpha}(1-\epsilon_I)(1-u_I)xv_s \geq 0,\\
&D^{\alpha}y_r|_{y_r=0} = \beta_s^{\alpha}(1-\epsilon_I)u_I xv_s + \beta_r^{\alpha}xv_r \geq 0,\\
&D^{\alpha}v_s|_{v_s=0} = k_s^{\alpha}(1-\epsilon_P)(1-u_P)y_s \geq 0,\\
&D^{\alpha}v_r|_{v_r=0} = k_s^{\alpha}(1-\epsilon_P)u_P y_s + k_r^{\alpha}y_r \geq 0,\\
&D^{\alpha}H|_{H=0} = s_H^{\alpha}\left(1+\gamma(y_s+y_r)\right) \geq 0.
\end{aligned} \tag{3}$$

Thus, by Corollary 2, the solution of model (1) will remain in R_+^6. □

3 Reproduction numbers and local stability of the disease-free equilibrium

In this section, we compute the reproduction number of model (1), R_0, and the local stability of its disease-free equilibrium. The basic reproduction number is defined as the number of secondary infections due to a single infection in a completely susceptible population.

We begin by considering two sub-models of model (1). Model (4) arises from model (1) by setting the variables concerning resistance dynamics (y_r and v_r) to zero, and model (10) follows from model (1) by setting the variables concerning sensitive dynamics (y_s and v_s) to zero.

We start by computing the reproduction number of model (4), R_s, using the next generation method [24]), and the local stabilities of its disease-free and the endemic equilibria. We have

$$\begin{aligned}
&\frac{d^\alpha x}{dt^\alpha} = \lambda^\alpha - d^\alpha x - \beta_s^\alpha (1-\epsilon_I) x v_s + r_1^\alpha x\left(1 - \frac{x+y_s}{T_{\max}}\right),\\
&\frac{d^\alpha y_s}{dt^\alpha} = \beta_s^\alpha (1-\epsilon_I)(1-u_I) x v_s - a_s^\alpha (1+\alpha_1 H) y_s,\\
&\frac{d^\alpha v_s}{dt^\alpha} = k_s^\alpha (1-\epsilon_P)(1-u_P) y_s - c_s^\alpha v_s,\\
&\frac{d^\alpha H}{dt^\alpha} = s_H^\alpha (1+\gamma y_s) - d_H^\alpha H - \beta_H^\alpha V_H H.
\end{aligned} \tag{4}$$

The disease-free equilibrium of model (4) is given by

$$P_0^1 = (x_0, y_{s_0}, v_{s_0}, H_0) = \left(\frac{T_{\max}(r_1^\alpha - d^\alpha + \sqrt{(r_1^\alpha - d^\alpha)^2 + \frac{4 r_1^\alpha \lambda^\alpha}{T_{\max}}})}{2 r_1^\alpha}, 0, 0, \frac{s_H^\alpha}{d_H^\alpha + \beta_H^\alpha V_H}\right). \tag{5}$$

Using the notation in [24] for system (4), the matrices for the new infection terms, F_s, and the other terms, V_s, are computed to be

$$\begin{aligned}
F_s &= \begin{pmatrix} 0 & \beta_s^\alpha (1-\epsilon_I)(1-u_I) x_0 \\ 0 & 0 \end{pmatrix},\\
V_s &= \begin{pmatrix} a_s^\alpha (1+\alpha_1 H_0) & 0 \\ -k_s^\alpha (1-\epsilon_P)(1-u_P) & c_s^\alpha \end{pmatrix}.
\end{aligned}$$

The associative basic reproduction number is thus

$$R_s = \rho\left(F_s V_s^{-1}\right) = \frac{(1-\epsilon_I)(1-u_I)(1-\epsilon_P)(1-u_P)\beta_s^\alpha k_s^\alpha x_0}{c_s^\alpha a_s^\alpha (1+\alpha_1 H_0)}, \tag{6}$$

where ρ indicates the spectral radius of $F_s V_s^{-1}$.

The linearization matrix of model (4) around the disease-free equilibrium, P_0^1, is

$$M_1 = \begin{pmatrix} -\sqrt{(r_1^\alpha - d^\alpha)^2 + \frac{4r_1^\alpha \lambda^\alpha}{T_{\max}}} & -\frac{-r_1^\alpha}{T_{\max}} x_0 & -\beta_s^\alpha (1-\epsilon_I) x_0 & 0 \\ 0 & -a_s^\alpha (1+\alpha_1 H_0) & \beta_s^\alpha (1-\epsilon_I)(1-u_I) x_0 & 0 \\ 0 & k_s^\alpha (1-\epsilon_P)(1-u_P) & -c_s^\alpha & 0 \\ 0 & s_H^\alpha \gamma & 0 & -d_H^\alpha - \beta_H^\alpha V_H \end{pmatrix}.$$

Stability of P_0^1 can be determined using the following lemmas.

Lemma 4 (Theorem 2, [25]) *Let* $\alpha (= \frac{p}{q})$ *where* $p, q \in \mathrm{Z}^+$ *and* $gdc(p,q) = 1$. *Define* $M = q$, *then the disease-free equilibrium* P_0^1 *of the system* (4) *is asymptotically stable if* $|\arg(\Lambda)| > \frac{\pi}{2M}$ *for all roots* Λ *of the following equation*:

$$\det\bigl(\operatorname{diag}\bigl[\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}\bigr] - M_1\bigr) = 0.$$

Lemma 5 *The disease-free equilibrium* P_0^1 *of the system* (4) *is unstable if* $R_s > 1$.

Proof Expanding $\det(\operatorname{diag}[\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}] - M_1) = 0$, we have the following equation in terms of Λ:

$$\begin{aligned} &\left[\Lambda^{M\alpha} + \sqrt{\bigl(r_1^\alpha - d^\alpha\bigr)^2 + \frac{4r_1^\alpha \lambda^\alpha}{T_{\max}}}\right]\bigl[\Lambda^{M\alpha} + d_H^\alpha + \beta_H^\alpha V_H\bigr] \\ &\quad \times \bigl[\Lambda^{2M\alpha} + \bigl(a_s^\alpha (1+\alpha_1 H_0) + c_s^\alpha\bigr)\Lambda^{M\alpha} + a_s^\alpha (1+\alpha_1 H_0) c_s^\alpha (1-R_s)\bigr] = 0. \end{aligned} \tag{7}$$

Now the arguments of the roots of the equation $\Lambda^{M\alpha} + \sqrt{(r_1^\alpha - d^\alpha)^2 + \frac{4r_1^\alpha \lambda^\alpha}{T_{\max}}} = 0$ are given by

$$\arg(\Lambda_k) = \frac{\pi}{M\alpha} + k\frac{2\pi}{M\alpha} > \frac{\pi}{M} > \frac{\pi}{2M},$$

where $k = 0, 1, \ldots, (M\alpha - 1)$.

Similarly arguments of the roots of the equation $\Lambda^{M\alpha} + d_H^\alpha + \beta_H^\alpha V_H = 0$ are all greater than $\frac{\pi}{2M}$.

Thus, using Lemma 4, we show that the disease-free equilibrium, P_0^1, of system (4) is unstable if there exists at least one root of the polynomial,

$$\Lambda^{2M\alpha} + \bigl(a_s^\alpha (1+\alpha_1 H_0) + c_s^\alpha\bigr)\Lambda^{M\alpha} + a_s^\alpha (1+\alpha_1 H_0) c_s^\alpha (1-R_s) = 0 \tag{8}$$

having an argument less than $\frac{\pi}{2M}$, for $R_s > 1$.

Using Descartes' rule of signs, we find that there is exactly one sign change of the equation:

$$\Lambda^{2M\alpha} + \left(a_s^\alpha(1+\alpha_1 H_0) + c_s^\alpha\right)\Lambda^{M\alpha} + a_s^\alpha(1+\alpha_1 H_0)c_s^\alpha(1-R_s) = 0 \tag{9}$$

for $R_s > 1$, thus there is exactly one positive real root of the aforesaid equation for which the argument is less than $\frac{\pi}{2M}$. Thus, if $R_s > 1$, the disease-free equilibrium P_0^1 of the system (4) is unstable. □

We proceed with the computation of the reproduction number of model 10, R_r, below

$$\begin{aligned}
\frac{d^\alpha x}{dt^\alpha} &= \lambda^\alpha - d^\alpha x - \beta_r^\alpha x v_r + r_1^\alpha x\left(1 - \frac{x+y_r}{T_{\max}}\right),\\
\frac{d^\alpha y_r}{dt^\alpha} &= \beta_r^\alpha x v_r - a_r^\alpha(1+\alpha_1 H) y_r,\\
\frac{d^\alpha v_r}{dt^\alpha} &= k_r^\alpha y_r - c_r^\alpha v_r,\\
\frac{d^\alpha H}{dt^\alpha} &= s_H^\alpha(1+\gamma y_r) - d_H^\alpha H - \beta_H^\alpha V_H H.
\end{aligned} \tag{10}$$

The disease-free equilibrium of model (10) is given by

$$P_0^2 = (x_0, y_{r_0}, v_{r_0}, H_0) = (x_0, 0, 0, H_0). \tag{11}$$

Using the notation in [24] on system (10), matrices for the new infection terms, F_r, and the other terms, V_r, are computed to be

$$\begin{aligned}
F_r &= \begin{pmatrix} 0 & \beta_r^\alpha x_0 \\ 0 & 0 \end{pmatrix},\\
V_r &= \begin{pmatrix} a_r^\alpha(1+\alpha_1 H_0) & 0 \\ -k_r^\alpha & c_r^\alpha \end{pmatrix}.
\end{aligned}$$

The associative basic reproduction number is thus

$$R_r = \rho\left(F_r V_r^{-1}\right) = \frac{\beta_r^\alpha k_r^\alpha x_0}{c_r^\alpha a_r^\alpha(1+\alpha_1 H_0)}, \tag{12}$$

where ρ indicates the spectral radius of $F_r V_r^{-1}$.

The linearization matrix of model (10) around the disease-free equilibrium, P_0^2, is

$$M_2 = \begin{pmatrix} -\sqrt{(r_1^\alpha - d^\alpha)^2 + \frac{4r_1^\alpha \lambda^\alpha}{T_{\max}}} & -\frac{-r_1^\alpha}{T_{\max}}x_0 & -\beta_r^\alpha x_0 & 0 \\ 0 & -a_r^\alpha(1+\alpha_1 H_0) & \beta_r^\alpha x_0 & 0 \\ 0 & k_r^\alpha & -c_r^\alpha & 0 \\ 0 & s_H^\alpha \gamma & 0 & -d_H^\alpha - \beta_H^\alpha V_H \end{pmatrix}.$$

Stability of P_0^2 can be determined using the following lemmas.

Table 1 Parameters used in the numerical simulations of model (1)

Parameter	Value (Units)	Reference
λ	7.5×10^5 (mL^{-1} day^{-1})	[5]
d	1.06×10^{-3} (day^{-1})	[6]
β_s	7.3×10^{-5} (mL day^{-1})	Estimated
ϵ_I	0.8	[6]
β_r	9.3×10^{-7} (mL day^{-1})	[27]
r_1	2.7 (day^{-1})	[6]
$T_{\max}$	4.016×10^6 (day^{-1})	[6]
u_I	1.2×10^{-4}	[4]
a_s	0.14 (day^{-1})	[5]
α_1	5×10^{-3}	[6]
a_r	0.14 (day^{-1})	[5]
k_s	45 (day^{-1})	[27]
ϵ_P	0.8	[6]
u_P	1.2×10^{-4}	[4]
k_r	45 (day^{-1})	[27]
c_s	6.2 (day^{-1})	[5]
c_r	6.2 (day^{-1})	[5]
s_H	10^4 (mL^{-1} day^{-1})	[28]
γ	2×10^{-8}	[6]
d_H	9×10^{-3} (day^{-1})	[6]
β_H	4.1×10^{-6} (mL day^{-1})	[6]
V_H	10^5 (mL day^{-1})	[6]

Lemma 6 (Theorem 2, [25]) *Let* $\alpha(=\frac{p}{q})$ *where* $p, q \in \mathrm{Z}^+$ *and* $gdc(p,q) = 1$. *Define* $M = q$, *then the disease-free equilibrium* P_0^2 *of the system* (10) *is asymptotically stable if* $|\arg(\Lambda)| > \frac{\pi}{2M}$ *for all roots* Λ *of the following equation*:

$$\det\bigl(\operatorname{diag}\bigl[\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}\bigr] - M_2\bigr) = 0.$$

Lemma 7 *The disease-free equilibrium* P_0^2 *of the system* (10) *is unstable if* $R_r > 1$.

Proof Expanding, $\det(\operatorname{diag}[\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}] - M_2) = 0$, we have the following equation in terms of Λ:

$$\begin{aligned}&\left[\Lambda^{M\alpha} + \sqrt{\bigl(r_1^\alpha - d^\alpha\bigr)^2 + \frac{4r_1^\alpha\lambda^\alpha}{T_{\max}}}\right]\bigl[\Lambda^{M\alpha} + d_H^\alpha + \beta_H^\alpha V_H\bigr]\\ &\quad\times\bigl[\Lambda^{2M\alpha} + \bigl(a_r^\alpha(1+\alpha_1 H_0) + c_r^\alpha\bigr)\Lambda^{M\alpha} + a_r^\alpha(1+\alpha_1 H_0)c_r^\alpha(1-R_r)\bigr] = 0.\end{aligned} \tag{13}$$

Now the arguments of the roots of the equation $\Lambda^{M\alpha} + \sqrt{(r_1^\alpha - d^\alpha)^2 + \frac{4r_1^\alpha\lambda^\alpha}{T_{\max}}} = 0$ are given by

$$\arg(\Lambda_k) = \frac{\pi}{M\alpha} + k\frac{2\pi}{M\alpha} > \frac{\pi}{M} > \frac{\pi}{2M},$$

where $k = 0, 1, \ldots, (M\alpha - 1)$.

Similarly the arguments of the roots of the equation $\Lambda^{M\alpha} + d_H^\alpha + \beta_H^\alpha V_H = 0$ are all greater than $\frac{\pi}{2M}$.

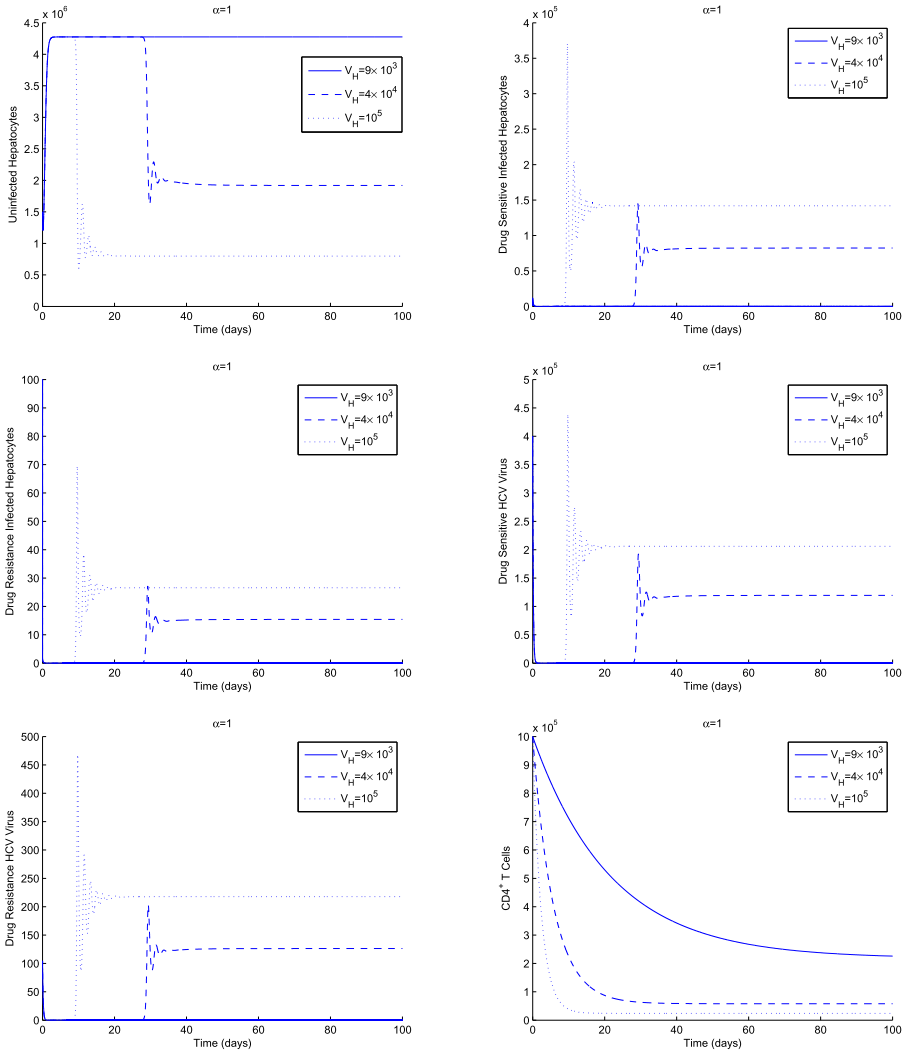

Figure 1 Dynamics of the variables of system (1) for different values of V_H, the HIV viral load, and $\alpha = 1.0$. Parameter values are in Table 1 and initial conditions are in the text.

Thus, using Lemma 6, we show that the disease-free equilibrium, P_0^2, of system (10) is unstable if there exists at least one root of the polynomial

$$\Lambda^{2M\alpha} + \left(a_r^\alpha(1+\alpha_1 H_0) + c_r^\alpha\right)\Lambda^{M\alpha} + a_r^\alpha(1+\alpha_1 H_0)c_r^\alpha(1-R_r) = 0 \tag{14}$$

having an argument less than $\frac{\pi}{2M}$, for $R_r > 1$.

Using Descartes' rule of signs, we find that there is exactly one sign change of the equation:

$$\Lambda^{2M\alpha} + \left(a_r^\alpha(1+\alpha_1 H_0) + c_r^\alpha\right)\Lambda^{M\alpha} + a_r^\alpha(1+\alpha_1 H_0)c_r^\alpha(1-R_r) = 0 \tag{15}$$

for $R_r > 1$, thus there is exactly one positive real root of the aforesaid equation for which the argument is less than $\frac{\pi}{2M}$. Thus, if $R_r > 1$, the disease-free equilibrium P_0^2 of the system (10) is unstable. □

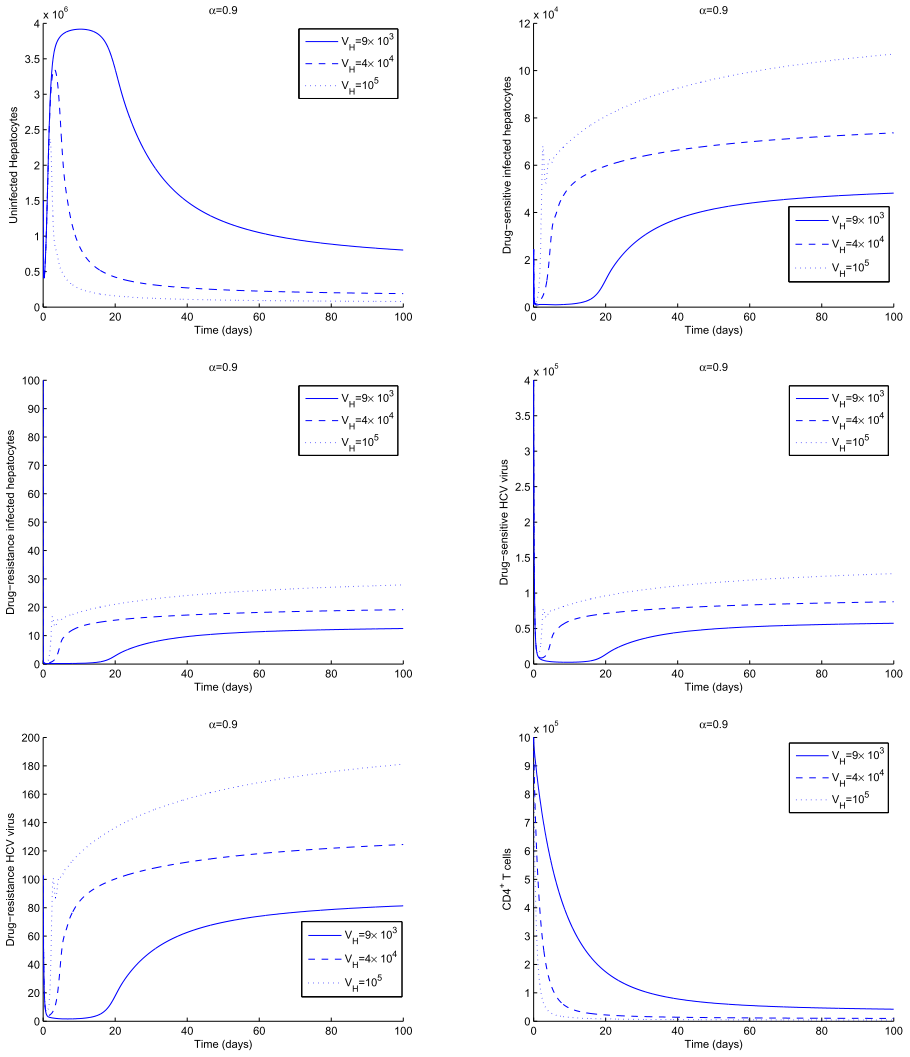

Figure 2 Dynamics of the variables of system (1) for different values of V_H, the HIV viral load, and $\alpha = 0.9$. Parameter values are in Table 1 and initial conditions are in the text.

The reproduction number of the full model (1), R_0 is calculated as follows. The disease-free equilibrium state, P_0, of model (1) is given by

$$P_0 = (x_0, y_{s_0}, y_{r_0}, v_{s_0}, v_{r_0}, H_0) = (x_0, 0, 0, 0, 0, H_0). \tag{16}$$

Using the notation in [24] on system (1), matrices for the new infection terms, F, and the other terms, V, are computed to be

$$F = \begin{pmatrix} 0 & 0 & \beta_s^\alpha (1-\epsilon_I)(1-u_I)x_0 & 0 \\ 0 & 0 & \beta_s^\alpha (1-\epsilon_I)u_I x_0 & \beta_r^\alpha x_0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

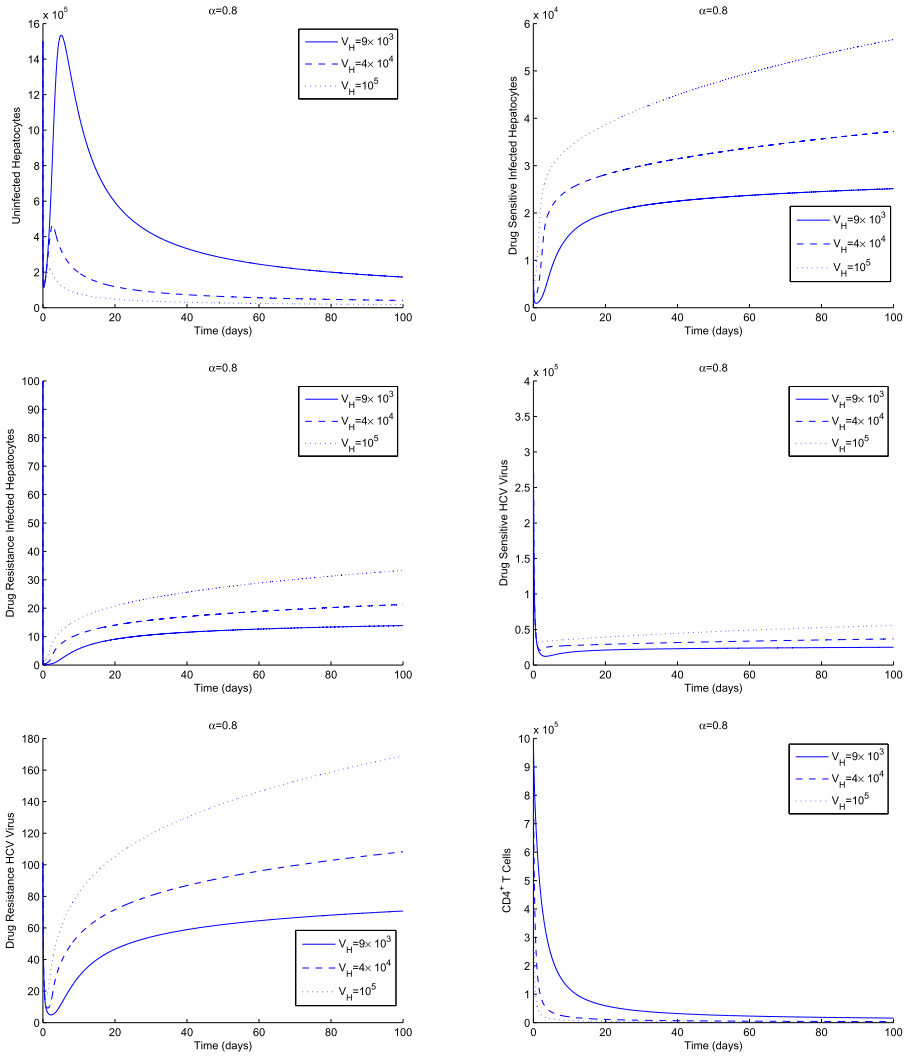

Figure 3 Dynamics of the variables of system (1) for different values of V_H, the HIV viral load, and $\alpha = 0.8$. Parameter values are in Table 1 and initial conditions are in the text.

$$V = \begin{pmatrix} a_s^\alpha(1+\alpha_1 H_0) & 0 & 0 & 0 \\ 0 & a_r^\alpha(1+\alpha_1 H_0) & 0 & 0 \\ -k_s^\alpha(1-\epsilon_P)(1-u_P) & 0 & c_s^\alpha & 0 \\ -k_s^\alpha(1-\epsilon_P)u_P & -k_r^\alpha & 0 & c_r^\alpha \end{pmatrix}.$$

The associative basic reproduction number is computed to be

$$R_0 = \rho\left(FV^{-1}\right) = \max(R_s, R_r), \tag{17}$$

where ρ indicates the spectral radius of FV^{-1}.

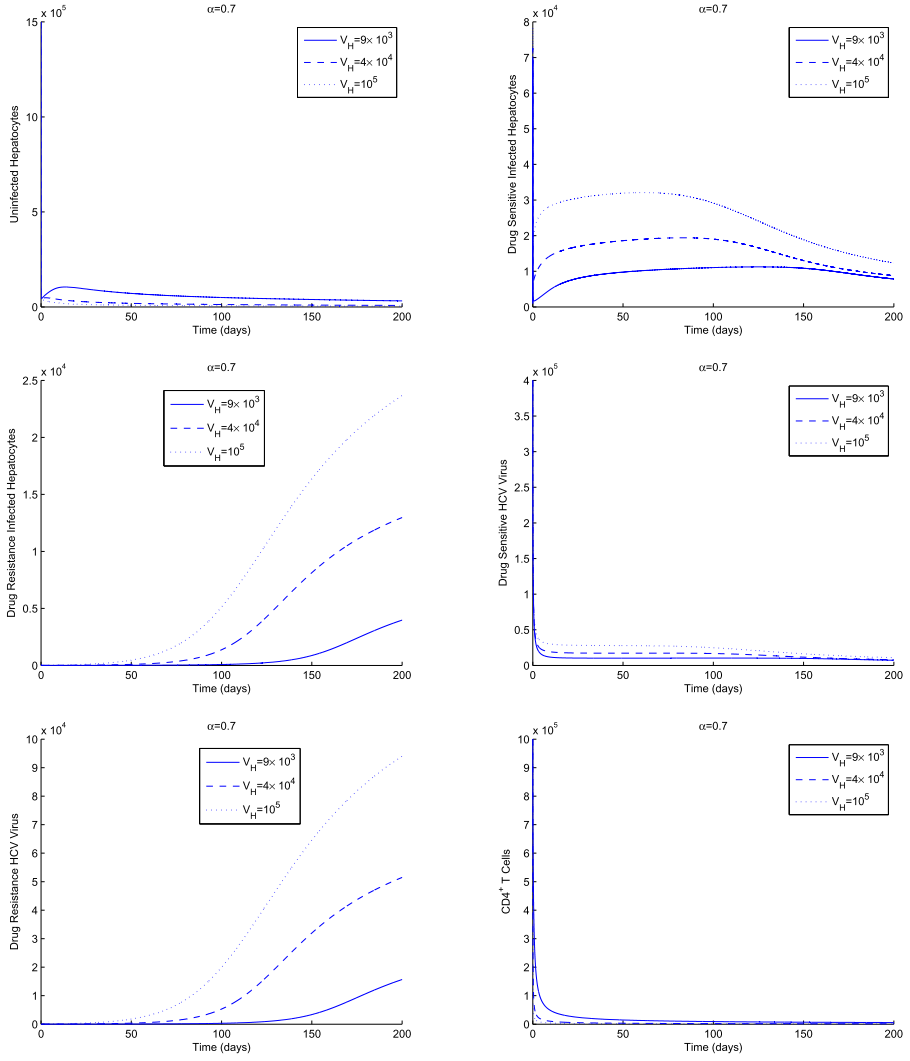

Figure 4 Dynamics of the variables of system (1) for different values of V_H, the HIV viral load, and $\alpha = 0.7$. Parameter values are in Table 1 and initial conditions are in the text.

The linearization matrix of model (1) around the disease-free equilibrium, P_0, is

$$M_3 = \begin{pmatrix} -\sqrt{(r_1^\alpha - d^\alpha)^2 + \frac{4r_1^\alpha \lambda^\alpha}{T\max}} & -\frac{-r_1^\alpha}{T\max}x_0 & -\frac{-r_1^\alpha}{T\max}x_0 & -\beta_s^\alpha(1-\epsilon_I)x_0 & -\beta_r^\alpha x_0 & 0 \\ 0 & -a_s^\alpha(1+\alpha_1 H_0) & 0 & \beta_s^\alpha(1-\epsilon_I)(1-u_I)x_0 & 0 & 0 \\ 0 & 0 & -a_r^\alpha(1+\alpha_1 H_0) & 0 & \beta_r^\alpha x_0 & 0 \\ 0 & k_s^\alpha(1-\epsilon_P)(1-u_P) & 0 & -c_s^\alpha & 0 & 0 \\ 0 & k_s^\alpha(1-\epsilon_P)u_P & k_r^\alpha & 0 & -c_r^\alpha & 0 \\ 0 & s_H^\alpha\gamma & s_H^\alpha\gamma & 0 & 0 & -d_H^\alpha - \beta_H^\alpha V_H \end{pmatrix}.$$

The stability of P_0 can be determined using the following lemmas.

Lemma 8 (Theorem 2, [25]) *Let* $\alpha(=\frac{p}{q})$ *where* $p, q \in \mathrm{Z}^+$ *and* $gdc(p,q) = 1$. *Define* $M = q$, *then the disease-free equilibrium* P_0 *of the system* (1) *is asymptotically stable if* $|\arg(\Lambda)| >$

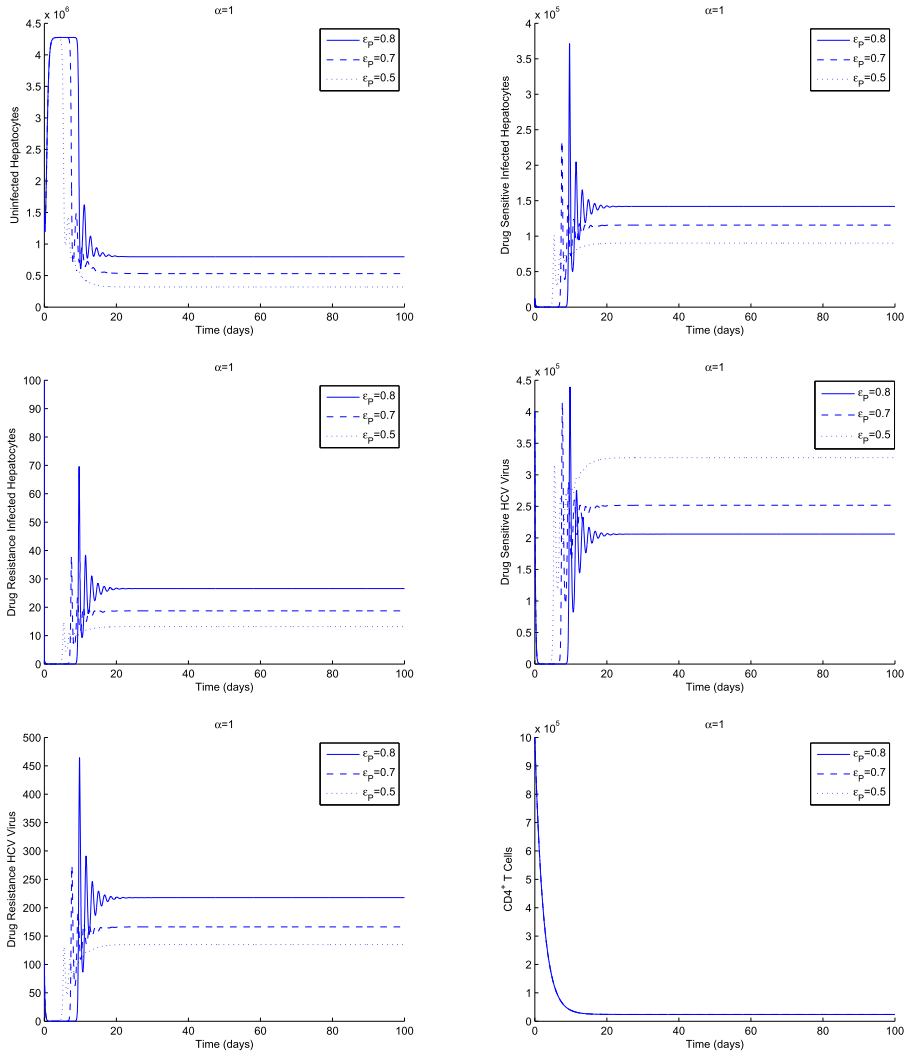

Figure 5 Dynamics of the variables of system (1) for different values of ϵ_P, the protease inhibitor drug efficacy, and $\alpha = 1.0$. Parameter values are in Table 1 and initial conditions are given in the text.

$\frac{\pi}{2M}$ *for all roots* Λ *of the following equation*:

$$\det\bigl(\operatorname{diag}\bigl[\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}\bigr] - M_3\bigr) = 0.$$

Lemma 9 *The disease-free equilibrium* P_0 *of the system* (1) *is unstable if* $R_0 > 1$.

Proof Expanding $\det(\operatorname{diag}[\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}\Lambda^{M\alpha}] - M_3) = 0$ we have the following equation in terms of Λ:

$$\begin{aligned}
&\left[\Lambda^{M\alpha} + \sqrt{\left(r_1^\alpha - d^\alpha\right)^2 + \frac{4r_1^\alpha\lambda^\alpha}{T_{\max}}}\right]\left[\Lambda^{M\alpha} + d_H^\alpha + \beta_H^\alpha V_H\right] \\
&\quad\times\left[\Lambda^{2M\alpha} + \left(a_r^\alpha(1+\alpha_1 H_0) + c_r^\alpha\right)\Lambda^{M\alpha} + a_r^\alpha(1+\alpha_1 H_0)c_r^\alpha(1-R_r)\right] \\
&\quad\times\left[\Lambda^{2M\alpha} + \left(a_s^\alpha(1+\alpha_1 H_0) + c_s^\alpha\right)\Lambda^{M\alpha} + a_s^\alpha(1+\alpha_1 H_0)c_s^\alpha(1-R_s)\right] = 0. \qquad (18)
\end{aligned}$$

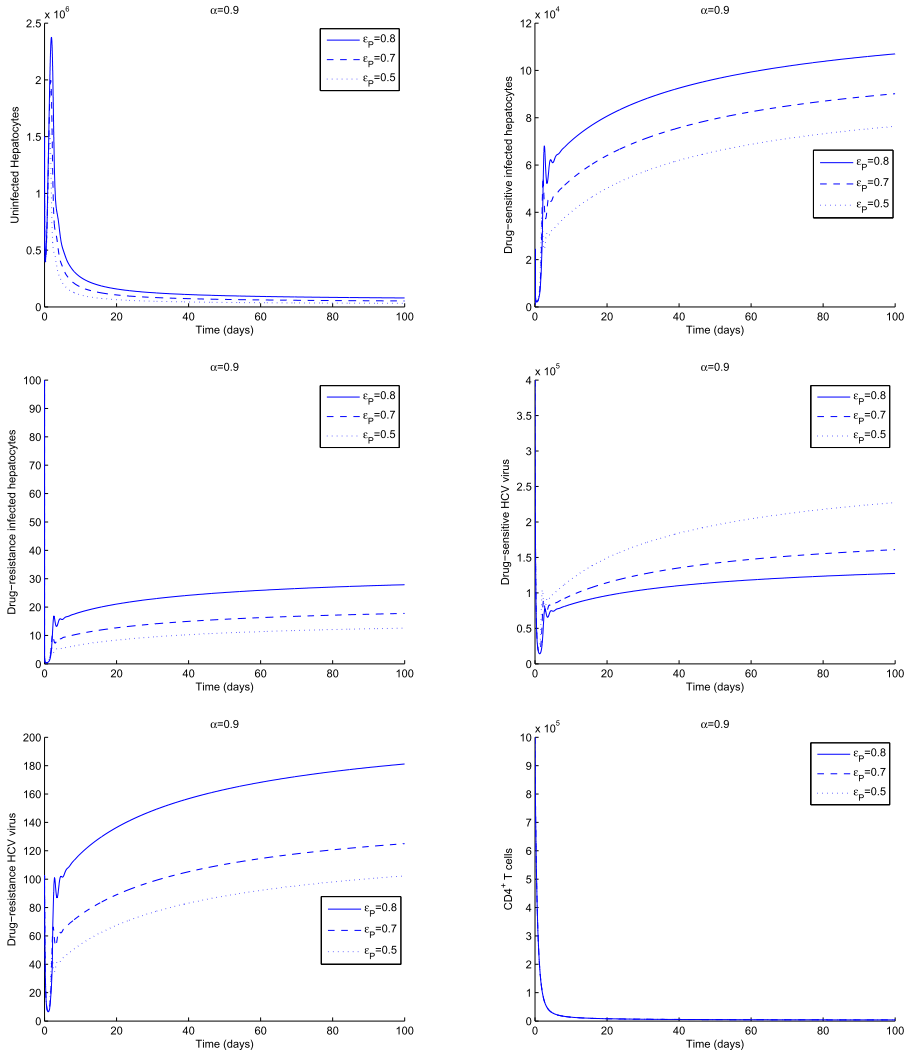

Figure 6 Dynamics of the variables of system (1) for different values of ϵ_P, the protease inhibitor drug efficacy, and $\alpha = 0.9$. Parameter values are in Table 1 and initial conditions are given in the text.

Now the arguments of the roots of the equation $\Lambda^{M\alpha} + \sqrt{(r_1^\alpha - d^\alpha)^2 + \frac{4r_1^\alpha \lambda^\alpha}{T_{\max}}} = 0$ are given by

$$\arg(\Lambda_k) = \frac{\pi}{M\alpha} + k\frac{2\pi}{M\alpha} > \frac{\pi}{M} > \frac{\pi}{2M},$$

where $k = 0, 1, \ldots, (M\alpha - 1)$.

Similarly the arguments of the roots of the equation $\Lambda^{M\alpha} + d_H^\alpha + \beta_H^\alpha V_H = 0$ are all greater than $\frac{\pi}{2M}$.

Thus, using Lemma 8, we show that the disease-free equilibrium, P_0, of system (1) is unstable if there exists at least one root of the polynomial

$$\Lambda^{2M\alpha} + \left(a_s^\alpha(1 + \alpha_1 H_0) + c_s^\alpha\right)\Lambda^{M\alpha} + a_s^\alpha(1 + \alpha_1 H_0)c_s^\alpha(1 - R_s) = 0 \tag{19}$$

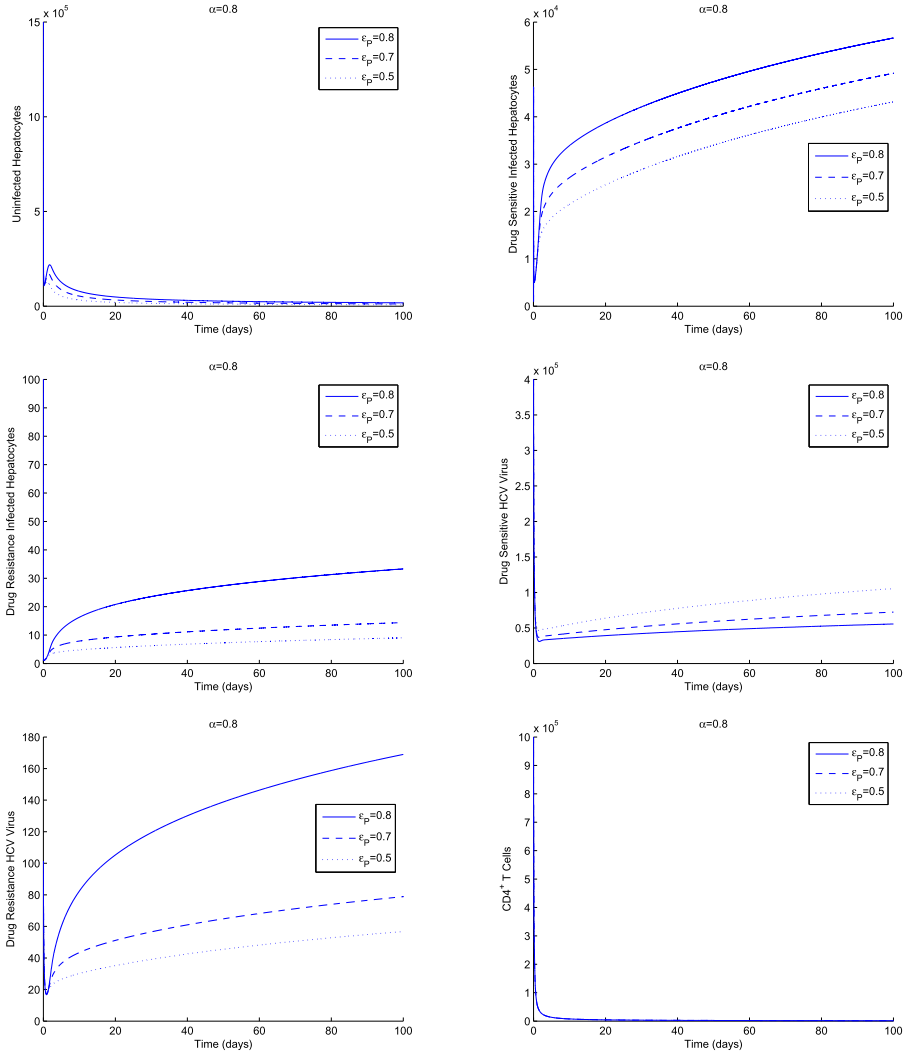

Figure 7 Dynamics of the variables of system (1) for different values of ϵ_P, the protease inhibitor drug efficacy, and $\alpha = 0.8$. Parameter values are in Table 1 and initial conditions are given in the text.

or

$$\Lambda^{2M\alpha} + \left(a_r^{\alpha}(1+\alpha_1 H_0) + c_r^{\alpha}\right)\Lambda^{M\alpha} + a_r^{\alpha}(1+\alpha_1 H_0)c_r^{\alpha}(1-R_r) = 0 \tag{20}$$

having an argument less than $\frac{\pi}{2M}$, for $R_s > 1$ or $R_r > 1$, respectively.

As shown previously, there is exactly one sign change for each polynomial when $R_s > 1$ and $R_r > 1$, respectively. Since $R_0 = \max(R_s, R_r)$, the disease-free equilibrium P_0 of the system (1) is unstable for $R_s > 1$ or $R_r > 1$. □

4 Numerical simulations

In this section, we show the results of the numerical simulations of model (1). We apply the Grünwald-Letnikov scheme to an approximation of the solutions of the model, where $h = 0.0005$ was the time step increment used [26]. The initial conditions are set

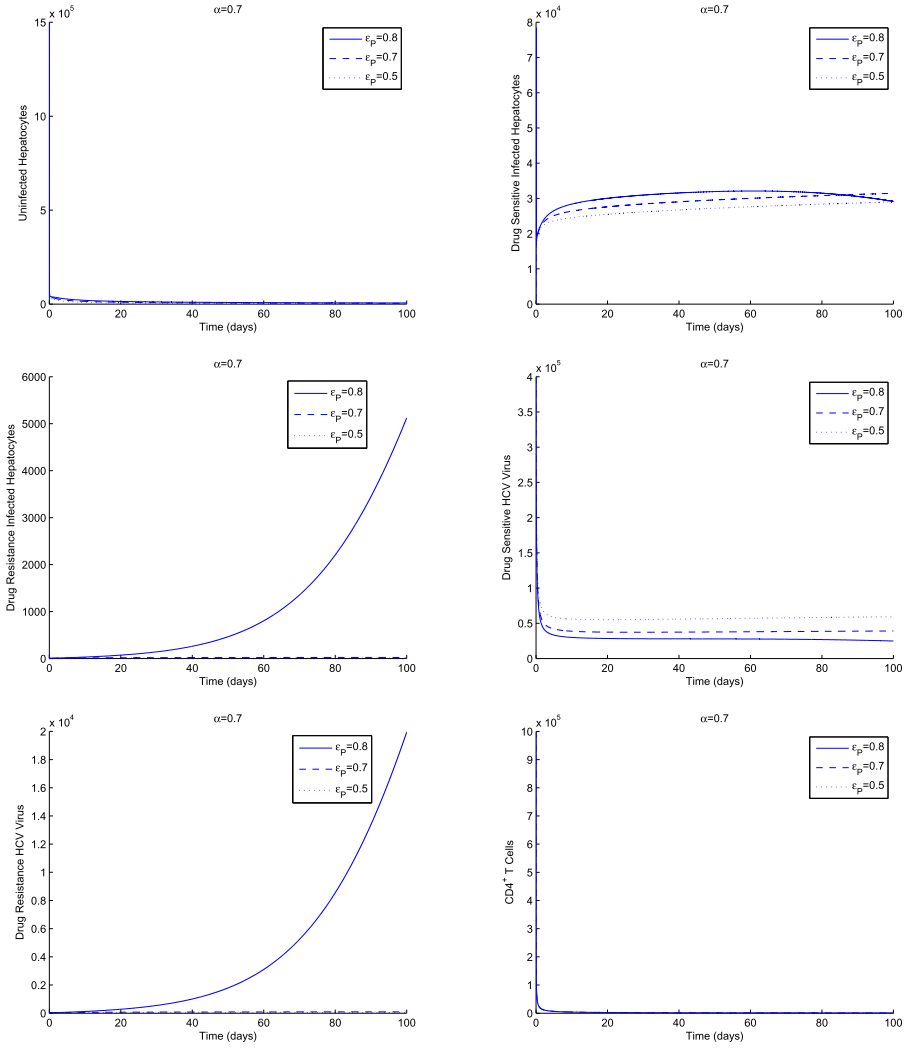

Figure 8 Dynamics of the variables of system (1) for different values of ϵ_P, the protease inhibitor drug efficacy, and $\alpha = 0.7$. Parameter values are in Table 1 and initial conditions are given in the text.

to $x(0) = 1.5 \times 10^6$, $y_s(0) = 10^3$, $y_r(0) = v_r(0) = 10^2$, $v_s(0) = 4 \times 10^5$ and $H(0) = 10^6$. The parameter values of the model (1) can be found in Table 1. The simulations were done for $\alpha \in (0, 1]$. We illustrate the results of the model including the figures for three values of α.

In Figures 1-4, we illustrate how HIV, V_H, influences the progression of HCV infection in the model (1), for four values of the order of the fractional derivative, α. We observe that, as the HIV viral load increases, the model bifurcates from a disease-free to an endemic equilibrium, for $\alpha = 1.0$. Moreover, the $CD4^+$ T cells count decreases, and the drug-sensitive and the drug-resistance infected hepatocytes and virus increase. Thus, higher HIV loads are directly associated to severe HCV infection. This is also observed for $\alpha = 0.9, 0.8, 0.7$. We note that for $\alpha = 0.9$ the model is already at the endemic state, which means that the progression of the coinfection is faster for smaller values of α. In Figure 1, by Lemma 1, the eigenvalues of the sys-

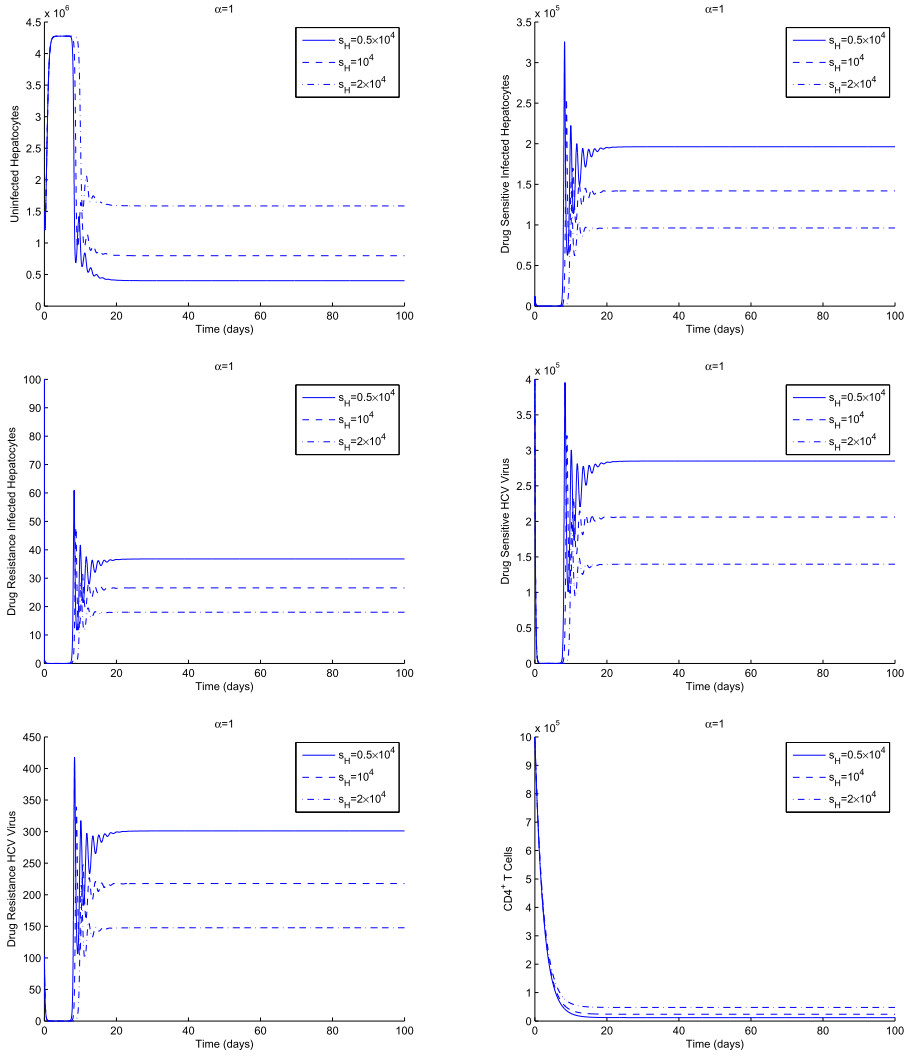

Figure 9 Dynamics of the variables of system (1) for different values of s_H, the CD4$^+$ T cells recruitment rate, and $\alpha = 1.0$. Parameter values are in Table 1 and initial conditions are given in the text.

tem around the disease-free equilibrium satisfy condition $|\arg(\lambda)| > \frac{\pi}{2M}$, for $\alpha = 1.0$. This translates in a value of the reproduction number, R_0, less than 1 ($R_0 = 0.2786$). This value is the maximum of the values of the reproduction numbers of the two submodels, the sensitive model ($R_s = 0.2786$), and the resistant model ($R_r = 0.0889$). For smaller values of α (Figures 2-4), the eigenvalues of the system do not comply to the previous condition, which translates in a value of $R_0 > 1$. The latter means that the disease-free equilibrium loses stability and an endemic equilibrium arises. The epidemic spreads.

The dynamics of the variables of system (1) for different values of ϵ_P, the protease inhibitor drug efficacy, and four values of α are depicted in Figures 5-8. When ϵ_P increases, the drug-sensitive HCV virus decrease, and the other variables increase, for the four values of α. We note that there is a slight increase in the number of HCV resistant virus, due to larger amounts of the drug. The latter is biologically reasonable. The bottom line shows

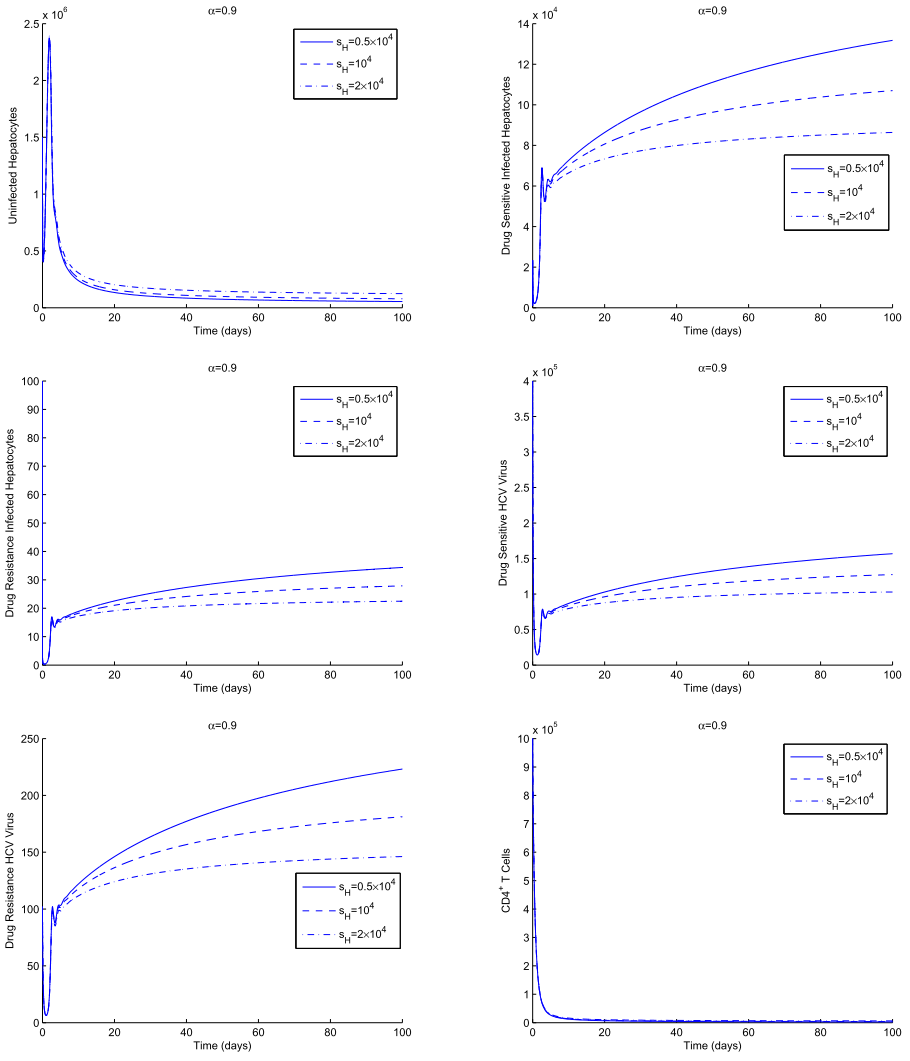

Figure 10 Dynamics of the variables of system (1) for different values of s_H, the CD4$^+$ T cells recruitment rate, and $\alpha = 0.9$. Parameter values are in Table 1 and initial conditions are given in the text.

that larger values of drugs diminish the severity of the HCV infection. In these figures, the value of the reproduction number, R_0, is always greater than 1. The disease propagates for all values of the order of the fractional derivative.

Figures 9-12 show the effect of the variation of the CD4$^+$ T cells recruitment rate in the dynamics of the coinfection, for four values of α. We observe that as the recruitment rate increases there is an overall increase in the patients' quality of life, since the severity of the disease, *i.e.*, the number of infected hepatocytes, decreases. This is similar for all values of α, though for $\alpha = 0.7$ this effect is harder to see.

In Figure 13, we observe the variation of the value of R_0 as a function of the HIV viral load, V_H, and of the drug-sensitive virus transmission rate, β_s. Higher viral loads promote the coinfection whenever the transmission rate is above a given threshold. This seems reasonable. In the presence of high viral loads, but controlled conditions (*e.g.*, the person

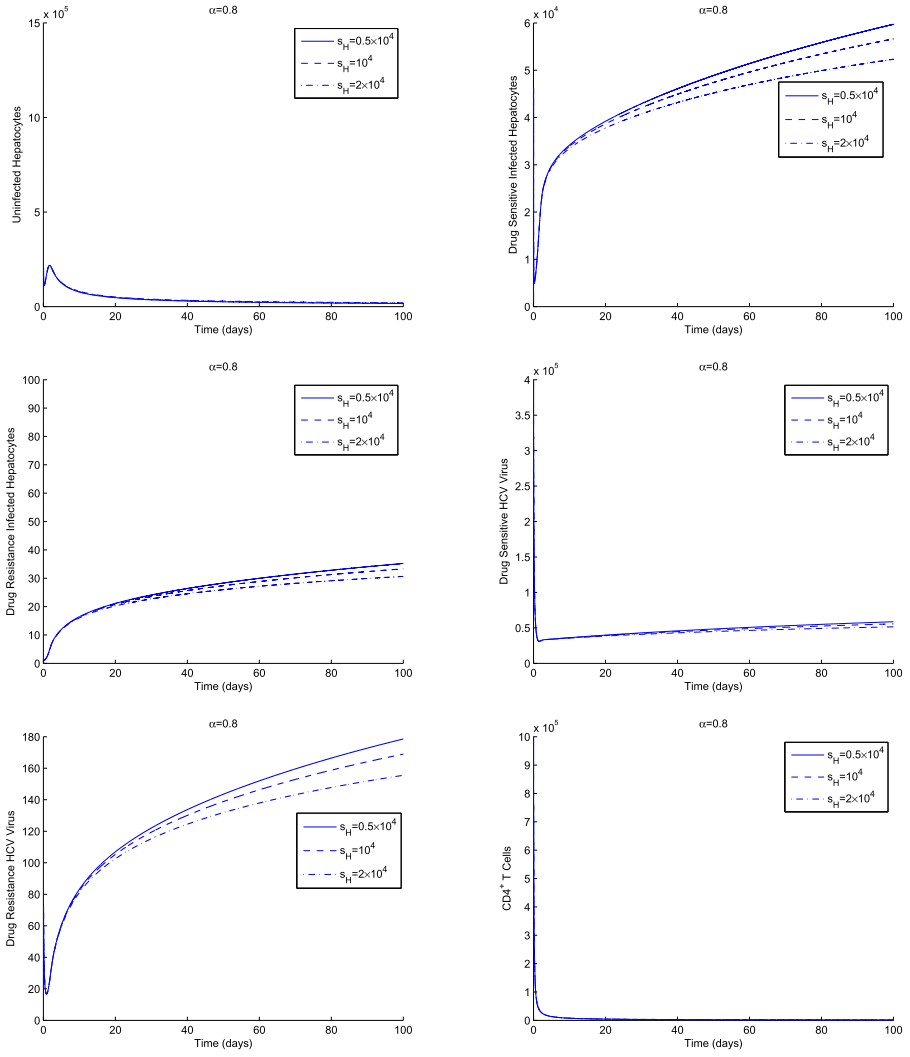

Figure 11 Dynamics of the variables of system (1) for different values of s_H, the CD4$^+$ T cells recruitment rate, and $\alpha = 0.8$. Parameter values are in Table 1 and initial conditions are given in the text.

does not have risk behaviors, the person is hospitalized, etc.), there is no propagation of the disease.

5 Conclusions

We derive a simple non-integer-order model for the coinfection of HIV and HCV, with treatment for HCV. We compute the basic reproduction number and the stability of the disease-free equilibrium. The simulations of the model reveal a strong dependency of the HCV infection progression on the HIV viral load. Higher HIV viral loads are associated with reduced immune response, which in turn translates in higher HCV viral loads. We have also considered the influence of the protease drug efficacy on the dynamics of the coinfection. We find that smaller values of this parameter are associated with a higher number of infected hepatocytes. The results of the models suggest that specific measures should be implemented, by the policy makers, in order to reduce HIV viral load

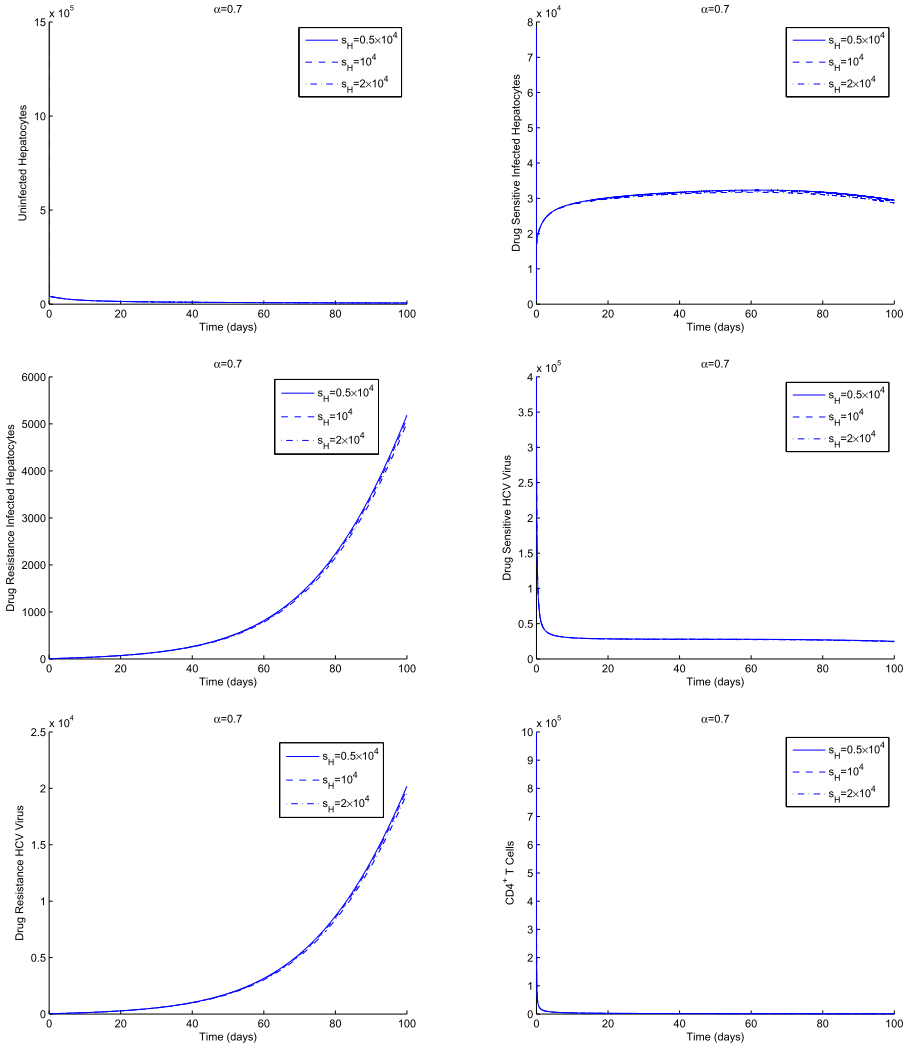

Figure 12 Dynamics of the variables of system (1) for different values of s_H, the $CD4^+$ T cells recruitment rate, and $\alpha = 0.7$. Parameter values are in Table 1 and initial conditions are given in the text.

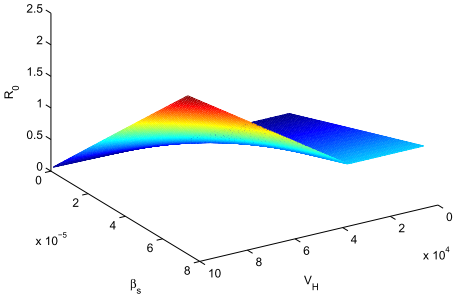

Figure 13 Variation of the value of the reproduction number R_0 as a function of the V_H, the HIV viral load and β_s, the drug-sensitive transmission rate, for $\alpha = 1.0$.

(preventive measures and treatment), and to treat HCV infection. The order of the fractional derivative seems to increase the severity of the disease, translated by higher HIV viral loads and infected hepatocytes. The results of the model are biologically reasonable.

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Competing interests
The authors declare that they have no competing interests.

Authors' contributions
The authors have contributed equally to this manuscript. They read and approved the final manuscript.

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